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EXAMINER	
STEADMAN, DAVID J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/955,737	CHOPRA ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-16,18-24,26,27 and 33-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-16,18-24,26,27 and 33-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/3/07 has been entered.

[2] Claims 12-16, 18-24, 26-27, and 33-43 are pending in the application.

[3] Applicant's amendment to the claims, filed on 10/3/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's amendment to the specification, filed on 10/3/07, is acknowledged.

[5] Receipt of a sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, and an amendment directing entry of the sequence listing into the specification, all filed on 10/3/07, is acknowledged.

[6] Applicant's arguments filed on 10/3/07 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Sequence Compliance

[8] In order to perfect sequence compliance, applicant is required to submit a statement that no new matter has been added to the specification by the paper copy of the sequence CRF filed on 10/3/07.

Claim Objections

[9] Claim 20 is objected to in the recitation of "the amino acid sequence of residues 58-447 of SEQ ID NO:1...the backbone atoms of said amino acids" and claims 21-22 are objected to in the recitation of "said amino acids..." In order to improve claim form, it is suggested that the claims use consistent terminology, *e.g.,* "the amino acid sequence of residues 58-447 of SEQ ID NO:1...the backbone atoms of said residues" in claim 20.

[10] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). See particularly the sequence recited in claim 12 part (ii) and claims 39-41. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing",

an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

Claim Rejections - 35 USC § 112, Second Paragraph

[11] Claims 12-16, 18-24, 26-27, and 33-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 12 (claims 13-16, 18-19, 33, 35, 37, 40, and 42-43 dependent therefrom) and 20 (claims 21-24, 26-27, 34, 36, 38-39, and 41 dependent therefrom) is unclear in the recitation of "providing a three dimensional structure..." followed by the step of "generating a three dimensional model..." It is unclear as to how "a three dimensional structure" is distinct from "a three dimensional model" as one of skill in the art would recognize the two phrases as being essentially synonymous and it is unclear to the examiner as to the intended difference(s) between "a three dimensional structure" and "a three dimensional model". It is suggested that applicant clarify the meaning of the noted phrases.

[b] Claims 42-43 are confusing as it is unclear as to how the additional method step of "providing a crystalline composition of BACE" is intended to be incorporated into the method of claim 12. For example, is this method step intended to be practiced prior to or following the step of "providing a three dimensional structure..."? It is suggested that

applicant clarify how the method steps of claims 42-43 are intended as being incorporated into the method of claim 12.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[12] Claims 12-15, 20-23, and 37-39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are drawn to a method of computerized, *i.e., in silico,* screening of agents that interact with BACE. The claims are viewed as an "abstract idea", *i.e.,* a "judicial exception", since the methods involve manipulation of data using a computer algorithm. According to MPEP 2106.IV, "A claimed invention is directed to a practical application of a 35 U.S.C. 101 judicial exception when it: (A) "transforms" an article or physical object to a different state or thing; or (B) otherwise produces a useful, concrete and tangible result". The claimed methods do not "transform" the data to a "different state or thing" and thus, to qualify as patent eligible subject matter, the claimed invention, as a whole, must accomplish a practical application. That is, it must produce a "useful, concrete and tangible result." *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368, 1373, 47 USPQ2d 1596, 1601-02 (Fed. Cir. 1998). Note that the "useful result" aspect of the practical application test requires significant functionality to be present. See *Arrhythmia Research Tech. v. Corazonix Corp.*, 958

F.2d 1053, 1057, 22 USPQ2d 1033, 1036 (Fed. Cir. 1992). In this case, the claimed methods do not produce a "useful, concrete and tangible result." Applicant may argue the claimed methods, being screening methods, would provide a result set of a number of lead compounds with an increased probability of binding to the protein whose structure was input. Applicant may further or optionally argue that the preambles of claims 12 and 20 are drawn to methods of identifying agents that interact with BACE. However, it is noted that there is no active method step that selects for those compounds that bind and/or modulate the protein represented by the 3-D model or structural coordinates that would provide a result set of a number of lead compounds with an increased probability of binding to the protein whose structure was input. For example, claim 12 recites "performing computer fitting analysis of a candidate agent...identifying the agent", where there is no active method step for identifying those candidate agents that are more likely to interact with BACE from those that are not. As such, the claimed methods are not deemed to have a "practical application" and thus the claimed invention is considered to be non-statutory subject matter.

Claim Rejections - 35 USC § 112, First Paragraph

[13] The written description rejection of claims 12-16, 18-24, 26-27, and 33-36 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. See paragraph 6 beginning at p. 3 of the Office action mailed on 10/3/06. Newly added claims 37-43 are included in the rejection. Thus, claims 12-16, 18-24, 26-27, and 33-43 are rejected.

RESPONSE TO ARGUMENT: Applicant argues (beginning at p. 11, top of the instant remarks) that the amended claims do not encompass widely variant species since the claims limit the sequence of BACE, the APP inhibitor, and the structural coordinates and any variation from the recited structural coordinates is limited by the recited root mean square deviation. Applicant clarifies the meaning of "relative structural coordinates" as recited in the claims. According to applicant, the Flower reference is not relevant to the rejection because the claims do not encompass homology models of structures created *de novo* and instead use models of BACE that are based on experimentally-determined structural coordinates. Applicant notes that the Flower reference discloses two methods for generating 3-D models for structure-based design – 1) producing a 3-D structure of a polypeptide by, *e.g.,* x-ray diffraction or NMR or 2) by homology modeling. According to applicant, both of these approaches were well-established at the time of the invention and the Flower reference acknowledges that the techniques involve automated methods that remove the tedium from the routine production of such 3-D models.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to adequately describe the genus of 3-D models as encompassed by the claims. There is no dispute that claim 12 (and claims dependent therefrom) specifies the that the BACE comprises residues 58-447 of SEQ ID NO:1, the APP inhibitor comprises SEVNStaVAEF, and the 3-D structure comprises the structure coordinates of those recited amino acids according to Figures 1A-1EEE ("Figure 1"). Also, there is no dispute that claim 20 (and claims dependent therefrom) specifies the

that the BACE "consists essentially of" residues 58-447 of SEQ ID NO:1 and the 3-D model of BACE has the structural coordinates of Figure 1. However, it is noted that in view of the recitation of the transitional phrase "comprises" in part (iii) of claim 12, the genus of 3-D structures encompasses additional amino acid sequence according to "residues 58-447 of SEQ ID NO:1", wherein the 3-D position(s) of the additional amino acids are undefined, and thus the genus of 3-D structures used in the claimed method encompasses homology models. Although the sequence of BACE has at least residues 58-447 of SEQ ID NO:1, claim 12 does not require that the resulting 3-D model of BACE maintains the 3-D positioning of these amino acids according to the structural coordinates of Figure 1. Thus, since the 3-D positioning of the remaining amino acids of the 3-D model are unlimited, the genus of 3-D models of BACE would appear to encompass widely variant 3-D models of BACE. Also, regarding the genus of 3-D models of claim 20, in view of the recitation of "comprises" in line 7 with respect to the genus of structural coordinates, the genus of 3-D models encompasses additional structural coordinates, *e.g.,* ligands, which is supported by claims 38-39. Thus, while applicant may argue that claims 20 and 37 limit the structural coordinates of the BACE to those of Figure 1, it is noted that the 3-D positioning of the APP inhibitor, which is an essential element of the 3-D model, is unlimited in the claims.

According to Flower ("Drug Design, Cutting Edge Approaches," Royal Society of Chemistry, Cambridge, UK, 2002; cited in a prior Office action), in addressing the use of homology models for identifying lead drugs, states "[p]roblems still exist, however: the fitting together of protein domains in a multi-domain protein, the determination of the

most likely conformation of protein loops, the correct positioning of amino acid side chains, flexible ligand docking - to name only a few" (p. 25, middle). Also, Lambert et al. (US Patent Application Publication 2004/0137518; cited in a prior Office action) teaches "[p]otential or existent homology models cannot provide the necessary degree of specificity" in the *in silico* design of modulators (p. 3, ¶[0017]), the teachings of which are undisputed by applicant. Applicant does not dispute the objective teachings of Flower and Lambert.

The specification discloses only a single representative species of such 3-D BACE models, *i.e.,* the 3-D model of BACE having the structural coordinates of Figure 1. According to MPEP § 2163.II.2.(a).ii), "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." As such, it would appear that the single disclosed species is insufficient to be representative of the attributes and features of the genus of 3-D BACE models as encompassed by the claims.

Although not expressly stated, it appears applicant takes the position that making and using homology models was routine at the time of the invention in view of the teachings of Flower. However, it appears applicant has mischaracterized the teachings of the Flower reference. The statement of Flower that "[i]t is now a well-established technique and automated methods that remove much of the tedium from the routine production of such models are now well known" appears to be related to generating a homology model using computerized techniques. This statement does not appear to address experimental techniques for determining a 3-D structure, *e.g.,* x-ray diffraction

or NMR. A proper reading of Flower by a skilled artisan shows that it is highly unpredictable as to whether or not homology models, the use of which is encompassed by the claims, maintain or represent a biologically relevant polypeptide structure.

Applicant argues (beginning at p. 14, middle of the remarks) the genus of "BACE" polypeptides is limited structurally limited by amendment and BACE polypeptides were known in the art at the time of the invention. Regarding the genus of "APP" polypeptides, applicant argues the genus is adequately described since APP polypeptides were well-known in the art at the time of the invention. Applicant further notes that the amino acid sequence disclosed by GenBank Accession Number CAA31380 has not been revised since 6/23/95, which is prior to the filing of the instant application.

To the extent the rejection is based on the description of the respective genus of "BACE" and "APP" polypeptides, this basis is withdrawn upon further consideration. The instant claim amendment limits the structures of the genus of BACE polypeptides to having the common structural element of "residues 58-447 of SEQ ID NO:1" and based upon applicant's Exhibits A to D (attached to the instant response), it appears that APP polypeptides, while varying in sequence, were well-known in the prior art at the time of the invention and would appear to satisfy the description requirement in view of the holding of *Capon v. Eshhar.*

With regard to the genus of recited crystals, applicant argues (beginning at p. 17 of the remarks) that since the claims are limited with respect to the structural coordinates, which are based on X-ray diffraction data of the disclosed crystal, the

genus of crystals is adequately described. According to applicant, the rejection would not apply to claims 42-43 in view Case 4 of the Trilateral Report.

Applicant's argument is not found persuasive. With regard to applicant's argument that the structural coordinates are limited to those obtained by X-ray diffraction using the disclosed crystal, it is noted that neither of claims 12 or 20 is so limited. As noted above, the 3-D model and corresponding structural coordinates of claim 12 is unlimited with respect to the amino acids not present in part (iii) of the claim. Also, claims 20 and 37, while limiting the structural coordinates of the 3-D model of BACE to Figure 1, are unlimited with respect to the additional elements, *e.g.,* 3-D model and corresponding structural coordinates of ligands, as encompassed by the genus. In this case, the specification discloses only a single representative species of 3-D models, *i.e.,* 3-D model of BACE in complex with SEVNStaVAEF having the structural coordinates of Figure 1, which are produced from a single representative species of crystals, *i.e.,* BACE protein prepared as disclosed at pp. 14-15 of the specification in complex with inhibitor SVENStaVAEF having the space group symmetry I222 and having vector lengths a=86.627, b=130.861 Å, and c=130.729 Å and $\alpha=\beta=\gamma=90^{\circ}$. While applicant attempts to rely on Case 4 of the Trilateral Report to support their position, it is noted that the crystal of Case 4 was limited to a specific protein, *i.e.,* protein P, while the protein of the crystal of claims 42-43 "comprises...residues 58-447 of SEQ ID NO:1". Also, the APP inhibitor of the "complex" of the crystal of claim 42 "comprises...SEVNStaVEF" and the crystal of claim 43 appears to be only a crystal of BACE itself, not in complex with the APP inhibitor as recited in claim 12. As noted by

McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990) at p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. *Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids*" (emphasis added). Thus, as acknowledged by McPherson, even minor alterations to a polypeptide may influence protein crystallization and thus it is highly unpredictable as to whether or not BACE and/or APP inhibitor as set forth in the claims can be crystallized at all, much less to achieve the recited space group and unit cell dimensions.

For at least the reasons presented above, it is the examiner's position that the specification fails to adequately describe the claimed invention.

[14] The scope of enablement rejection of claims 12-16, 18-24, 26-27, and 33-36 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. See paragraph 7 beginning at p. 8 of the Office action mailed on 10/3/06. Newly added claims 37-43 are included in the rejection. Thus, claims 12-16, 18-24, 26-27, and 33-43 are rejected.

RESPONSE TO ARGUMENT: Applicant argues (beginning at p. 18, top of the instant remarks) the amended claims do not encompass widely variant 3-D models since the claims limit the sequence of BACE, the APP inhibitor, and the structural

coordinates and any variation from the recited structural coordinates is limited by the recited root mean square deviation. Applicant clarifies the meaning of "relative structural coordinates" as recited in the claims.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to enable the full scope of the claimed invention as encompassed by the claims. There is no dispute that claim 12 (and claims dependent therefrom) specifies the that the BACE comprises residues 58-447 of SEQ ID NO:1, the APP inhibitor comprises SEVNStaVAEF, and the 3-D structure comprises the structure coordinates of those recited amino acids according to Figures 1A-1EEE ("Figure 1"). Also, there is no dispute that claim 20 (and claims dependent therefrom) specifies the that the BACE "consists essentially of" residues 58-447 of SEQ ID NO:1 and the 3-D model of BACE has the structural coordinates of Figure 1. However, it is noted that in view of the recitation of the transitional phrase "comprises" in part (iii) of claim 12, the genus of 3-D structures encompasses additional amino acid sequence according to "residues 58-447 of SEQ ID NO:1", wherein the 3-D position(s) of the additional amino acids are undefined, and thus the genus of 3-D structures used in the claimed method encompasses homology models. Although the sequence of BACE has at least residues 58-447 of SEQ ID NO:1, claim 12 does not require that the resulting 3-D model of BACE maintains the 3-D positioning of these amino acids according to the structural coordinates of Figure 1. Thus, since the 3-D positioning of the remaining amino acids of the 3-D model are unlimited, the genus of 3-D models of BACE would appear to encompass widely variant 3-D models of BACE. Also, regarding the genus of 3-D

models of claim 20, in view of the recitation of "comprises" in line 7 with respect to the genus of structural coordinates, the genus of 3-D models encompasses additional structural coordinates, *e.g.,* ligands, which is supported by claims 38-39. Thus, while applicant may argue that claims 20 and 37 limit the structural coordinates of the BACE to those of Figure 1, it is noted that the 3-D positioning of the APP inhibitor, which is an essential element of the 3-D model, is unlimited in the claims.

Further, it is noted that claims 12 and 20 require the steps of "providing a three dimensional structure...". According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action." MPEP 2164.08 states, "...the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims...claims are to be given their broadest reasonable interpretation that is consistent with the specification." In light of the specification (*e.g.,* paragraphs 28-29 at p. 8), it would appear that the step of "providing..." is intended as encompassing crystallizing a polypeptide to obtain (or provide) the structural coordinates of the crystallized polypeptide.

Applicant argues (beginning at p. 19 of the remarks) BACE amino acid sequence and biological function were well-characterized at the time of the invention, particularly with respect to residues that are necessary for biological activity. Applicant further argues that techniques for generating mutants and techniques for high resolution solution structure and molecular modeling were well-known at the time of the invention. Thus, according to applicant, in view of the teachings of the specification, a skilled

artisan would have been able to make the full scope of the claimed invention without requiring undue experimentation.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to enable the full scope of the claimed invention, particularly with respect to the crystals and 3-D models as encompassed by the claims. While there is no dispute that at least one sequence of BACE and its function was well-characterized at the time of the invention, the scope of crystals and 3-D models as used in the claims encompass crystals and 3-D structures of BACE polypeptides that were not known or disclosed in the specification and the specification fails to provide guidance for crystallizing other BACE polypeptides and determining their structure(s) and further whether a 3-D model represents a biologically-active BACE polypeptide in accordance with the asserted utility of designing agents for interaction with BACE. Further, the specification fails to provide guidance for using those 3-D models of BACE that do not represent a biologically-relevant model of a polypeptide that has the activity of a BACE and agents that would be designed using methods employing such models. While applicant argues that because BACE was characterized, a skilled artisan would alter the structure outside of those residues involved in binding or catalysis. However, as noted above, the specification fails to provide guidance or expectation that altering a BACE, even outside of those ligand binding or catalytic residues, will achieve diffraction-quality crystals and/or maintain the 3-D conformation of a biologically active BACE.

Applicant argues that methods for making structural models by experimental methods and by homology modeling were well-established techniques and not highly

unpredictable. Applicant argues that once the BACE structural coordinates are identified as set forth in Figure 1, models can be routinely generated within the rms as recited in the claims. According to applicant, the Lambert et al. reference supports this position.

Applicant's argument is not found persuasive. Although applicant argues experimental techniques, *e.g.,* crystallography, for determining the structure of a protein were well-established at the time of filing, applicant provides no objective evidence to support such a position. To the contrary, such methods were highly unpredictable as evidenced by the objective references of Branden et al., Drenth, Kierzek et al. (cited in a prior Office action), and McPherson (*supra*). Also, it is noted that while applicant argues the models are limited to having the "experimentally-determined" structural coordinates of Figure 1 and variants thereof within the recited rms deviation, the claims are not so limited. See discussion above regarding the scope of the claims. And, while there is no dispute that the structural coordinates of Figure 1 would be useful for designing agents that bind to BACE, it is highly unpredictable as to whether or not all 3-D models as encompassed by the claims would, particularly as these models would be generated by homology modeling, which, as evidenced by Flower and Lambert et al., it is highly unpredictable as to whether such models will be useful in the rational design of modulator compounds since there is no way to predict or even test whether or not the resulting homology model maintains a biologically relevant conformation.

In this case, the specification discloses only a single working example of a method for producing a 3-D model of BACE using experimental techniques, *i.e.,* a crystal of the BACE protein prepared as disclosed at pp. 14-15 of the specification in

complex with inhibitor SVENStaVAEF having the space group symmetry I222 and having vector lengths a=86.627, b=130.861 Å, and c=130.729 Å and $\alpha=\beta=\gamma=90^{\circ}$ and the specification discloses only a single working example of a crystallization method to achieve such crystal, *i.e.,* the method disclosed at pp. 14-15, paragraphs 41-44 of the specification, and only a single working example of a 3-D model of BACE produced by such techniques, *i.e.,* the 3-D model of BACE in complex with SVENStaVAEF having the structural coordinates of Figure 1. Other than this single working example of a method for producing a 3-D model using experimental techniques and a single working example of a 3-D model, the specification fails to disclose any working examples of a homology model as encompassed by the claims and further fails to provide specific guidance regarding other methods or alterations to the disclosed method for making any BACE 3-D model as encompassed by the claims. While methods of structural determination by protein crystallography were known at the time of the invention, it was not routine in the art to produce and use all 3-D models of any IL-13 polypeptide as encompassed by the claims.

Applicant argues at length (beginning at p. 21 of the remarks) regarding the enablement of "BACE" polypeptides. Applicant's argument regarding the tolerance of BACE polypeptides to amino acid replacement is not found persuasive, in view of the instant amendment to limit the breadth of the recited BACE polypeptide to "comprising" or "consisting essentially of...residues 58-447 of SEQ ID NO:1, this basis of the rejection is withdrawn. The scope of "APP" polypeptides as a basis of the instant rejection is also withdrawn. Applicant provides evidence that APP polypeptides were

known in the art at the time of the invention (see Exhibits A to D attached to the instant response) and the prior art characterizes the BACE cleavage site of APP. Moreover, it is noted that, in view of the disclosure of the specification, the scope of "APP" polypeptides does not appear to encompass any and all mutants, but only those APPs that have "conservative substitutions".

Applicant argues *de novo* crystallization and resolution of the BACE structure is not required to practice the claimed invention and even if the claims would require *de novo* crystallization, such is not undue experimentation. Although applicant acknowledges crystallography is "a tedious and time-consuming process," this does not mandate a conclusion that undue experimentation is required to practice the full scope of the claimed invention. According to applicant the Flower and Branden et al. references indicate that automated methods are available for speeding up protein crystallography.

Applicant's argument is not found persuasive. As noted above, in view of the disclosure of the specification, the claims are clearly intended to encompass crystallography as the "providing..." step. As noted in the prior Office action, such techniques are highly unpredictable as evidenced by, *e.g.,* Branden et al., Drenth, and Kierzek et al.

It appears applicant has mischaracterized the teachings of Flower and Branden et al. It is acknowledged that at the time of the invention, automated processes were available for purifying proteins and to generate "many more [crystallization] trials...and at much more accurately defined conditions than is the case for manual crystallizations."

However, there is no evidence of record that such automated processes can be used to predict the conditions that will lead to successful crystallization of BACE, much less the conditions for crystallization of all BACE polypeptides as encompassed by the claims. As noted in the prior Office action and undisputed by applicant, Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20, 2001), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). See also the teachings of McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990), which states (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly

arriving at a just assignment of importance for each factor is substantial for several reasons. *Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids*" (emphasis added). Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual." Thus, in view of these teachings, a skilled artisan would recognize there is a *high* level of unpredictability in making a protein crystal. It is noted that there is no objective evidence of record that would suggest that protein crystallography is routine and if applicant maintains the position that achieving diffraction-quality crystals of a protein was routine in the art at the time of the invention, applicant is requested to provide evidence to support this position.

Thus, at least for the reasons of record and the reasons set forth above, the specification fails to enable the full scope of the claimed invention. The examiner has properly considered all Factors of *In re Wands,* and when the evidence is taken as a whole (MPEP 2164.05), it is the examiner's position that the specification in view of the prior art fails to enable the full scope of the claimed invention.

Claim Rejections - 35 USC § 102/103

[15] The rejection of claims 12-16, 18-19, 33, and 35 under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tang et al. (US Patent 6,545,127) is withdrawn in view of amendment to claim 12 requiring the APP inhibitor of the 3-D structure of claim 12 to having the sequence "SEVNStaVAEF", whereas the inhibitor of the 3-D structure of Tang et al. is disclosed as being OM99-2, which appears to be distinct from the APP inhibitor sequence of claim 12. See particularly abstract, Figure 3B, and Example 9 beginning at column 29 of Tang et al. See also applicant's discussion of the differences between OM99-2 and SEVNStaVAEF at p. 27, middle of the instant remarks.

[16] The rejection of claims 20-21, 23-24, 26-27, 34, and 36 under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tang et al. (US Patent 6,545,127; "Tang") is maintained for the reasons of record and the reasons set forth below. Since the examiner's response to applicant's argument relies on the reference of Bridges et al. (Peptides 27:1877-1885, 2006) as described below,

the examiner has included the reference of Bridges et al. in the rejection as an evidentiary reference.

As noted in a prior Office action, the reference of Tang teaches crystallization of human BACE (referred to as memapsin 2 by Tang) co-complexed with a BACE inhibitor, OM99-2 (Example 9), determination of the 3-D structure of human BACE (Example 9), and a method of computer-assisted rational drug design using the 3-D structure obtained thereby, including analysis of the interaction between the compound and the 3-D structure (columns 13-14, Example 10). Tang teaches the design of BACE inhibitors using data obtained from crystal structure data, synthesis of BACE inhibitors so designed (Example 7), and inhibition of BACE-mediated APP cleavage using the synthesized inhibitors (Example 8). Newly added claim 38 is included in the instant rejection as the 3-D model of Tang is disclosed as having the structural coordinates of OM99-2 (Example 9, beginning at column 29), which is disclosed as being a peptide based on the amino acid sequence of Swedish mutant of APP (Example 7, beginning at column 22), which is interpreted herein as being encompassed by the term "an APP inhibitor" in claim 38.

RESPONSE TO ARGUMENT: Applicant argues the claimed invention is distinguished over Tang because: 1) the amino acid sequence of BACE in claim 20 "is closed with respect to including additional residues from human BACE" outside of the recited range of amino acids 58-447 of SEQ ID NO:1; and 2) the 3-D structure of Tang was derived from a crystal having a different space group and unit cell dimensions as that disclosed herein.

Applicant's argument is not found persuasive. Regarding argument 1), while the examiner acknowledges the transitional phrase "consisting essentially of" in claim 20, in this case, this transitional phrase fails to limit the 3-D model of BACE to exclude additional amino acids for reasons that follow. According to MPEP 2111.03, "For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." Also, it is noted that MPEP 2111.01 states, "During examination, the claims must be interpreted as broadly as their terms reasonably allow". In this case, the neither the specification nor the claims provides a *clear* indication as to what the "basic and novel characteristics actually are", thus, the term "consisting essentially of" has been broadly, but reasonably interpreted as "comprising". Even assuming *arguendo* the transitional phrase "consisting essentially of" is interpreted as "consisting of", it is noted that claim 20 further recites the transitional phrase "comprising" in the phrase "wherein the three dimensional structure comprises the relative structural coordinates" and according to MPEP 2111.03, " the use of "consists" in the body of the claims d[oes] not limit the open-ended "comprising" language in the claims". Accordingly, the examiner has interpreted claim 20 as encompassing a 3-D model of BACE *including* amino acids 58-447, but that is not *limited* to amino acids 58-447. Consequently, the 3-D model of Tang is encompassed by the claims.

Regarding argument 2), it is noted that the post-filing reference of Bridges et al. (Peptides 27:1877-1885, 2006; "Bridges") provides evidence to the contrary. Bridges

teaches a comparison of the 3-D structure derived from a crystal of BACE1:MSP-1, which appears to be the same as the crystal disclosed herein, and the 3-D structure of BACE1 in complex with OM99-2 (p. 1880, left column, middle). According to Bridges, the structures shared "a RMS of Cα atoms of 0.6 Å" (p. 1880, column 1, middle). As such, even though there is no dispute that the crystals have distinct unit cell dimensions and space group symmetries, the resulting 3-D structure of Tang is encompassed by claims 20 and 21 in view of the recited variation of the backbone atoms of "not more than 1.5 Å" in claim 20 or "not more than 1.0 Å" in claim 21.

Claim Rejections - 35 USC § 103

[17] The rejection of claim(s) 12-16, 18-24, 26-27, and 33-36 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (*supra*) in view of In re Gulack 217 USPQ 401 (Fed. Cir. 1983) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. See paragraph 10 beginning at p. 20 of the Office action mailed on 10/3/06. Newly added claims 37-39 are included in the rejection. Thus, claims 12-16, 18-24, 26-27, and 33-39 are rejected.

RESPONSE TO ARGUMENT: Applicant argues the claimed invention is distinguished over Tang because: 1) the claims recite the use of a 3-D model of BACE that has a distinct BACE amino acid sequence, a distinct inhibitor, and is derived from a crystal having distinct space group and unit cell dimensions; 2) the allegedly distinct 3-D model imposes a change in the screening procedure from that of Tang, providing structural information of an agent, which is functional information and would not have

been obtained using the method of Tang; and 3) the method requires "concrete steps", which "alter the steps performed by a computer program", *e.g.,* energy calculations and the structural coordinates of the candidate agent during docking.

Applicant's argument is not found persuasive. Regarding argument 1), the amino acid sequence of the model of Tang is encompassed by claims 12 and 20 (and claims dependent therefrom) in view of the recitation of the transitional phrase "comprises" in claim 12, part (i) and the transitional phrases "consisting essentially of" and "comprises" in claim 20. Also, that 3-D structures are derived from distinct crystals provides no indication that the 3-D structures themselves are patentably distinct for reasons described above relating to claims 20-21.

Even so, the examiner does not dispute differences between the 3-D model of claims 12 and 22 and the 3-D model of Tang. For example, the model of claim 12 requires a complex of BACE and SEVNStaVAEF, which does not appear to be taught or suggested by Tang. Also, in view of the teachings of Bridges (*supra*), the model of Tang does not appear to have a RMS deviation from the backbone atoms of "not more than 0.5 Å".

However, the noted differences between the recited model of the claims and the model of Tang appear to be a function of the descriptive material, *i.e.,* the structural coordinate data corresponding to the respective 3-D model. Put another way, the difference(s) between the method of Tang and the claimed method appears to be in the structural coordinate data, *i.e.,* the descriptive material. While there is no dispute that differences between the structural coordinates of Tang et al. and those disclosed in

Figure 1 may exist, such differences do not necessarily impart patentability to the claimed methods. In analyzing the structural coordinate data as a distinguishing feature over the prior art, it is acknowledged that "[t]he Patent and Trademark Office (PTO) must consider all claim limitations when determining patentability of an invention over the prior art," and "may not disregard claim limitations comprised of printed matter." *In re Lowry*, 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994). Since the difference between Tang et al. and the claimed methods appears to be limited to the structural coordinate descriptive material, in determining whether the descriptive material imparts patentability to a claimed invention, "the critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate." *In re Gulack*, 703 F.2d 1381, 1386, 217 USPQ 401, 404 (Fed. Cir. 1983).

Regarding arguments 2) and 3), as noted in a prior Office action, in Gulack, the Court held that nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability. The key factor in analyzing the obviousness of these claims over the prior art is the determination that the computer algorithm used to identify compounds that may bind BACE is a known algorithm and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. In this case, the claimed invention appears to rely on a known, unmodified algorithm for processing the Figure 1 data. Thus, the question of

obviousness appears to turn on whether the Figure 1 data is functional or non-functional descriptive material.

Here, applicant appears to take the position that the differences between the Figure 1 data and the structural coordinate data of Tang ultimately result in differences in how a computer would function or perform. According to the specification, "With the aid of specifically designed computer software, such crystallographic data can be used to generate a three dimensional structure of the molecule or molecular complex" (p. 8, paragraph 29) and "Computer fitting analyses utilize various computer software programs that evaluate the 'fit' between the putative active site and the identified agent by (a) generating a three dimensional model of the putative active site of a molecule or molecular complex using homology modeling or the atomic structural coordinates of the active site, and (b) determining the degree of association between the putative active site and the identified agent. Three dimensional models of the putative active site may be generated using any one of a number of methods known in the art" (p. 10, paragraph 33). Thus, according to the specification, it is the "computer software programs" that perform data processing to evaluate the fit, not the structural coordinate data itself. As such, one of ordinary skill in the art would recognize that the actual processing is due to the software programs and the computer as the structural data itself does not appear to execute any instructions or perform processing steps that alter the function of the algorithm and/or the computer. Moreover, there is no evidence of record to support applicant's allegation that the Figure 1 data alter the processing steps of the known algorithm and/or computer upon which the structural coordinate data is stored. As noted

in MPEP 716.01(c).II, "The arguments of counsel cannot take the place of evidence in the record".

As noted in the prior Office action, data, which are fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps, do not impose a change in the processing steps and are thus nonfunctional descriptive material. A method of using a known comparator for its known purpose to compare data sets does not become nonobvious merely because new data becomes available for analysis. Since the Figure 1 data is fed into a known algorithm whose purpose is to compare or modify the data using a series of processing steps, the Figure 1 data would not appear to alter the function of the computer itself as would a computer program or a data structure that imparts functionality, which are both considered to be functional descriptive material. "'Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability'" and "Although the printed matter must be considered, in that situation it may not be entitled to patentable weight." *Gulack*, 703 F.2d at 1385, 217 USPQ at 404. Consequently, as noted above, since the Figure 1 data shares no functional relationship with the computer upon which it stored, the data would appear to be "a compilation or mere arrangement of data", which is considered to be non-functional descriptive material. Since the data is considered to be non-functional descriptive material, the Figure 1 data has not been accorded patentable weight.

Examiner Comment/Clarification

[18] Claims 16, 19, 24, and 27 recite "contacting the agent with BACE...", which step has been interpreted as encompassing an *ex silico* step requiring physical contact between the agent and BACE, *e.g.,* in an *in vitro* assay.

Conclusion

[19] Status of the claims:

Claims 12-16, 18-24, 26-27, and 33-43 are pending.

Claims 12-16, 18-24, 26-27, and 33-43 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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